UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte IMRE KOVESDI and PAUL D. KESSLER

Appeal No. 2004-1259
Application No. 09/832,355

ON BRIEF

Before ADAMS, MILLS and GRIMES, Administrative Patent Judges.

MILLS, Administrative Patent Judge.

DECISION ON APPEAL

This is a decision on appeal under 35 U.S.C. §134 from the examiner's final rejection of claims 1-7, 9, 12, 16-19, 30-41 and 43-46. Claims 8, 13 and 20-28 have been withdrawn from consideration by the examiner as directed to a non-elected species. Answer, page 5. We take no position with respect to the patentability of the non-elected species. See Ex parte Ohsaka, 2 USPQ2d 1460, 1461 (Bd. Pat. App. & Int. 1987). Original claims 10, 11, 14, 15, 29 and 42 were cancelled in an Amendment filed February 24, 2003.

Claims 1, 9, 12 and 17 are illustrative of the claims on appeal and read as follows:

1. A fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain.

9. The fusion protein of claim 1, wherein the fusion protein is more angiogenic than a protein consisting essentially of the first peptide portion and/or is more angiogenic than a protein consisting essentially of the second peptide portion.

12. The fusion protein of claim 9, wherein blood vessels resulting from administration of the fusion protein to a mammalian host are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration of endothelial cells, or any combination thereof, than blood vessels resulting from administration of a protein consisting essentially of the first peptide portion.

17. The fusion protein of claim 1, wherein the second peptide portion comprises a peptide which promotes blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability, or any combination thereof.

The references cited by the examiner are:

Gill et al. (Gill)	6,291,667	Sept. 18, 2001
Rockwell et al. (Rockwell)	5,874,542	Feb. 23, 1999
Davis et al. (Davis)	WO 00/37642	Jun. 29, 2000

Yoon et al. (Yoon), "Cloning and Cytotoxicity of Fusion Proteins of EGF and Angiogenin," Life Sciences, Vol. 64, No.16, pp. 1435-1445 (1999)

References cited by Appellants are:

N. Ferrara, "VEGF: an update on biological and therapeutic aspects," Curr. Opinion Biotech., Vol. 11, pp. 617-624 (2000)

Souttou, et al., “Pleiotrophin Induces Angiogenesis: Involvement of the Phosphoinositide-3 Kinase but Not the Nitric Oxide Synthase Pathways,” J. of Cell. Phys., Vol. 187, pp. 59-64 (2001)

E. Papadimitriou, et al., “Endothelial Cell Proliferation induced by HARP: Implication of N. or C terminal peptides,” Biochem. Biophys. Res. Comm., Vol. 274, pp. 242-248 (2000)

R. Choudhuri, et al., “An angiogenic role for the neurokines, midkine and pleiotrophin in tumorigenesis,” Can. Res., Vol. 57, pp. 1814-1819 (1997)

Imai, et al., “Osteoblast Recruitment and Bone Formation Enhanced by Cell Matrix associated Heparin-binding Growth-associated Molecule (HB-GAM),” J. Cell Biol., Vol. 143, No. 4, pp. 1113-1128 (1998)

T.F. Deuel, et al., “Pleiotrophin: A Cytokine with Diverse Functions and a Novel Signaling Pathway,” Arch. Biochem. Biophys., Vol. 397, No. 2, pp. 162-171 (2002)

Grounds of Rejection

Claim 31 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

Claims 1-7, 9, 12, 16-19, 30-41 and 43-46 stand rejected under 35 U.S.C. § 112, first paragraph for lack of enablement and lack of written description.

Claims 1-4, 9, 16-19, 32-34, 39-40 and 43-45 stand rejected under 35 U.S.C. § 102(a), as anticipated by Davis.

Claims 1-5, 9, 17, 18, 32-34, 41 and 43-46 stand rejected under 35 U.S.C. § 103(a), as obvious over Yoon in view of either or both of Gill and Rockwell.

We reverse the enablement and written description rejections and affirm the prior art rejections.

Claim Grouping

The appellants argue that the claims do not stand or fall together. Brief, pages 3-4. However, with respect to the prior art rejections, appellants have not separately argued the patentability of any individual claims. Brief, pages 9-10. 37 CFR § 1.192(c)(7) (1997) (Claims stand or fall together "unless a statement is included that claims the claims of the group do not stand or fall together and, in the argument under paragraph (c)(8) of this section, appellant explains why the claims of the group are believed to be separately patentable." (Emphasis added.)). Claims not separately argued stand or fall with those that are separately argued. In re Sernaker, 702 F.2d 989, 991, 217 USPQ 1,3, (Fed. Cir. 1983). We decide this appeal on the basis of claim 1 with respect to the prior art rejections. In Young, 927 F.2d 588, 590, 18 USPQ2d 1089, 1091 (Fed. Cir. 1991). Rejections for lack of enablement and written description are reversed.

DISCUSSION

Background

The claimed invention is directed to a fusion protein comprising a first non-heparin-binding VEGF-A peptide portion, or a peptide portion that exhibits at least about 80% homology to a VEGF-A peptide portion, and a second non-VEGF peptide portion covalently associated with the first peptide portion, which first and second peptide portions separately promote angiogenesis or bone growth, and wherein the second peptide portion lacks a collagen binding domain. Specification, pages 1-2. Such a fusion protein is useful for promoting angiogenesis, bone growth, and/or wound healing. Specification, page 2.

According to the specification, by "non-heparin-binding it is meant that less than about 5% of the VEGF peptide portion of the fusion protein should be bound to heparin-containing sites at a given moment after administration to or expression in a mammalian host (compared to, e.g., about 50-70% binding for $VEGF_{165}$, and about 90-100% for $VEGF_{189}$). More preferably, the VEGF peptide portion exhibits no apparent affinity for heparin, as exhibited by VEGF-C, non-heparin binding P1GFs, VEGF-R and, more preferably, $VEGF_{121}$." Specification, page 15.

The non-VEGF peptide portion can be any suitable peptide portion including a non-VEGF factor, preferably which is capable of promoting angiogenesis, bone growth, or wound healing. Specification, page 17. By non-VEGF portion, it is meant that the

second peptide portion exhibits less than about 20%, preferably less than 10%, and more preferably less than 5% amino acid sequence identity to the VEGF peptide portion and preferably exhibits at least one distinct biological function from that associated with the VEGF peptide, preferably a function related to angiogenesis, bone growth, and/or wound healing. Specification, page 18.

35 U.S.C. § 112, first paragraph

Claim 31 stands rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention.

It is the examiner's position that (Answer, page 7):

> Claim 31 has been amended to recite that the fusion protein comprises an N-terminal truncated form of HBNF or MK including "at least about 60% of the wild-type HBNF or MK amino acid sequence.["] Appellants point to paragraph [0063] for support for this limitation. However, examination of that paragraph reveals only disclosure of about "70% *or less*, more preferably about 65% or less, and even more preferably about 60% or less..." There is no disclosure of the now claimed "at least about 60%", which is equivalent to '60% or more', which would include species with greater than 70%, the highest number recited.

It is well settled that persons skilled in this art must reasonably recognize in the originally filed application a description of the invention defined by the claims which establishes that appellants was in possession of the invention, including all of the limitations thereof, as of the filing date. See, e.g., In re Alton, 76 F.3d 1168, 1175-76,

37 USPQ2d 1578, 1583-84 (Fed. Cir. 1996); Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1116-17 (Fed. Cir. 1991); In re Kaslow, 707 F.2d 1366, 1373, 217 USPQ 1089, 1096 (Fed. Cir. 1983); In re Wertheim, 541 F.2d 257, 262-65, 191 USPQ 90, 96-98 (CCPA 1976).

Our reviewing court has held in Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1562, 19 USPQ2d 1111, 1116 (Fed. Cir. 1991) that

> [a] fairly uniform standard for determining compliance with the "written description" requirement has been maintained throughout: "Although [the applicant] does not have to describe exactly the subject matter claimed, ... the description must clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989) (citations omitted). "[T]he test for sufficiency of support in a parent application is whether the disclosure of the application relied upon 'reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter.'" Ralston Purina Co. v. Far-Mar-Co, Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Upon our review of the specification, particularly at paragraph [0063], we find the specification reasonably conveys to the artisan that the inventor had possession at the time the application was filed. The examiner argues there is no disclosure of the now claimed “at least about 60%, which is equivalent to '60% or more', which would include species with greater than 70%, the highest number recited.” We disagree.

The specification, page 27, numbered paragraph [0063], indicates that the HBNF-MK second peptide portion can include any suitable HBNF-MK peptide or fragment. Preferably the HBNF-MK is the naturally occurring HBNF. Thus, it would reasonably appear from the specification that the full length HBNF peptide is

contemplated. While, the specification also provides for preferred truncated forms of HBNF peptide having various percentage amounts of the HBNF peptide, the specification does not exclude the full length peptide and thus would appear to reasonably support a claim to "at least about 60% of the wild-type HBNF or MK amino acid sequence."

The rejection of claim 31 for lack of written description is reversed.

Enablement and Written Description

Claims 1-7, 9, 12, 16-19, 30-41 and 43-46 stand rejected under 35 U.S.C. §112, first paragraph for lack of enablement and lack of adequate written description.

The examiner raises several issues of lack of written description and enablement with respect to the claims. We address them, in turn, below.

1. **Lack of Enablement VEGF Protein**

The examiner argues that the claims in the application "are extremely broad, encompassing a fusion protein of any possible VEGF protein that does not bind to heparin, to any other cytokine with any angiogenic or bone growth activity. Overall, the specification does not teach how to make and use the invention in a manner commensurate in scope with the claims, and does not provide an adequate written description to support the claimed scope." Answer, pages 7-8.

According to the examiner, claims 1 and 43, for example recite that the VEGF portion may have bone growth promoting activity, such is not an art recognized property of VEGF, and is neither described or enabled by the specification as originally filed. Answer, page 8.

We agree with appellants that the examiner has failed to provide sufficient evidence to establish a prima facie case of lack of enablement. We begin with claim interpretation. As set forth in In re Hiniker Co., 150 F.3d 1362, 1369, 47 USPQ2d 1523, 1529 (Fed. Cir. 1998), "[t]he name of the game is the claim." Since claim interpretation will normally control the remainder of the decisional process, in considering the issue of patentability "analysis begins with a key legal question – what is the invention claimed?" Panduit Corp. v. Dennison Mfg. Co., 810 F.2d 1561, 1567-1568, 1 USPQ2d 1593, 1597 (Fed. Cir. 1987). An analysis of whether the claims under appeal are supported by an enabling disclosure requires a determination of whether that disclosure contains sufficient information regarding the subject matter of the appealed claims as to enable one skilled in the pertinent art to make and use the claimed invention.

In the present case, claim 1 requires that the first and second peptide portions either separately promote angiogenesis **or** bone growth. A patent need not teach and preferably omits, what is well known in the art. Although not explicitly stated in section 112, to be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without "undue experimentation." In re Vaeck, 947 F.2d 488, 495, 20 USPQ2d 1438, 1444 (Fed. Cir. 1991); In

re Wands, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988). Nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. In re Marzocchi, 439 F.2d 220, 223, 169 USPQ 367, 369 (CCPA 1971).

In our view, the examiner has not provided sufficient argument or evidence to support the position that the specification does not enable or describe VEGF peptides which promote angiogenesis or bone growth. Because the claim merely requires that the VEGF peptides possess one or the other of the functions of angiogenesis or bone growth, the specification need only enable one or the other of these functions. The specification, particularly at pages 2-4 and pages 7-14, describes a representative group of VEGF peptides having angiogenesis promoting activity. As indicated by the cited prior art, VEGF peptides as a class are well known to those of ordinary skill in the art. See, e.g., Rockwell, columns 1-2 and Gill, column 2. Moreover, the specification at pages 13 and 14, numbered paragraphs 36 and 37, describes how one of ordinary skill in the art can test for and confirm that peptides possess angiogenesis promoting or bone growth promoting activities.

The examiner has not provided a careful consideration of the level of ordinary skill in the art, or appropriate evidence to establish that any experimentation required to determine angiogenesis promoting and bone growth promoting activities, in view of the knowledge in the art of VEGF peptides, would have been undue experimentation. As we have found that the examiner has not established a prima facie case of lack of

enablement in the first instance, we do not reach appellants' evidence in support of enablement.

Written Description

35 U.S.C. §112, ¶ 1 has been interpreted to require a written description requirement separate and apart from the enablement requirement. See Amgen Inc. v. Hoechst Marion Roussel, Inc., 314 F.3d 1313, 1330 [65 USPQ2d 1385] (Fed. Cir. 2003) (citing Vas-Cath Inc. v. Mahurkar, 935 F.2d 1555, 1563 [19 USPQ2d 1111] (Fed. Cir. 1991)) (holding construction of §112, ¶ 1 requires separate written description and enablement requirements). In re Curtis, 354 F3d 1347, 69 USPQ2d 1274 (Fed. Cir., 2004).

It is well-settled that the written description requirement of 35 U.S.C. § 112, first paragraph, can be satisfied without express or explicit disclosure of a later-claimed invention. See, e.g., In re Herschler, 591 F.2d 693, 700, 200 USPQ 711, 717 (CCPA 1979): "The claimed subject matter need not be described in haec verba to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." (citations omitted). See also Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

We apply the relevant law above to the facts before us. In the present case, with respect to the written description aspect of the rejection, we find the specification to be sufficiently detailed, specifically describing a large group of representative compounds which fall within the scope of the pending claims. The claims only require that the VEGF peptides possess one or the other of the angiogenesis promoting and bone growth promoting activities. The specification, however, would appear to describe HBNF peptides, which according to appellants and the specification, possess bone growth promoting properties. Specification, page 27.[1]

In our view appellants have described the claimed subject matter in the specification clearly enough that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented the claimed subject matter. In view of the above, this aspect of the enablement and written description rejections is reversed.

2. **Lack of Written Description and Enablement non-VEGF Protein**

The examiner also argues that the specification does not provide an adequate written description of or enablement of the scope of claimed "second non-VEGF peptide portion" with angiogenesis or bone growth promoting activity in general, nor with the scope of HBNF in particular. Answer, page 8. The examiner argues (Answer, page 8):

[1] The examiner has presented no evidence that HBNF was not known to those of ordinary skill in the art to possess bone growth promoting properties.

> [t]he written description and enablement are not commensurate in scope with any and all possible non-VEGF peptides with angiogenesis or bone growth promoting activity. The specification has defined such in a manner that is so broad that any possible functional equivalent is encompassed.

In addition, the examiner argues that "[m]any of the cytokines listed as being angiogenic at paragraph [0050] are not recognized in the art as being angiogenic, for example, TNF alpha is an inflammatory, not an angiogenic cytokine, TGF beta is a cell growth inhibitor and not an angiogenic cytokine, IGF, while pleiotrophic [sic], is not considered in the art to be an angiogenic factor, etc." Id., pages 8-9.

The examiner takes the position that, "[w]ith the exception of the known forms of angiogenic cytokines, including HBNF, and art recognized derivatives thereof the skilled artisan cannot envision the detailed chemical structure of the encompassed proteins, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation." Answer, page 9.

Appellants argue that, "Section 112, first paragraph, is satisfied by the disclosure of a representative number of species. A 'representative number of species' means that the species which are adequately described are representative of the entire genus. Thus, when there is a substantial variation within the genus, one can describe a sufficient variety of species to reflect the variation within the genus." Brief, page 5, citing MPEP 2163.

The examiner responds, arguing that "given the breadth of the claims, which when read in view of the specification encompass all functional equivalents of any bone growth promoting protein or angiogenic protein, coupled with the fact that numerous of

the cytokines specifically recited in the specification as having such activity do not have either activity, the written description and enablement in the specification do not support the breadth of the claims." Answer, page 18.

The examiner's rebuttal position fails for several reasons. First, the examiner has failed to consider and address appellants' argument concerning the specification's disclosure of a representative number of species to support the entire genus. Next, we find no evidence of record provided by the examiner which supports the position of the examiner that cytokines such as TNF alpha, TGF beta and IGF do not possess angiogenic properties as set forth in appellants' specification. Bone growth promoting substances are referenced in the specification at pages 33-34, paragraphs [0073-0075]. The examiner has the burden in the first instance to put forth evidence of lack of enablement.

Patent examiners, in relying on what they assert to be general knowledge to negate patentability, must articulate that knowledge and place it of record, since examiners are presumed to act from the viewpoint of a person of ordinary skill in the art in finding relevant facts, assessing the significance of the evidence, and making the ultimate determination. Failure to do so is not consistent with either effective administrative procedure or effective judicial review, examiners cannot rely on conclusory statements, but must set forth the rationale on which they rely. See In re Lee, 277 F.3d 1338, 1343-1344, 61 USPQ2d 1430, 1433-1434 (Fed. Cir. 2002). Thus, it is improper to rely on the "common knowledge and common sense" of a person of

ordinary skill in art to find an invention unpatentable, since the factual questions are material to patentability, and cannot be resolved on subjective belief and unknown authority. Id.

The examiner has failed to put forth evidence indicating that one of ordinary skill in the art would have understood that TNF alpha, TGF beta and IGF do not possess angiogenic properties, especially in view of appellants' statements in the specification and reference to patents and publications in the specification to the contrary. Nor has the examiner provided appropriate evidence to support her position that the bone growth promoting peptides referenced in the specification would not have possessed the functions indicated therein. It is not appellants' burden to bring forth such evidence until the examiner establishes a prima facie case of lack of enablement.

Finally, the examiner's suggestion of the possible existence of non-operational embodiments within the scope of the claims does not necessarily mean the claims are unpatentable. Texas Instruments v. U.S. International Trade Commission, 805 F.2d 1558, 1562, 231 USPQ 833, 835 (Fed. Cir 1986). "Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid... . [I]f the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid." EMI Group North America Inc. v. Cypress Semiconductor Corp., 60 USPQ2d 1423 (CA FC 2001); Atlas Powder Co. v. E.I. Du Pont De Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414(Fed. Cir. 1984). The examiner

has not established with appropriate evidence that any inoperable embodiments are within the scope of the claimed non-VEGF second peptide or that any such embodiments would have been significant in number to call into question the patentability of the claims.

As with the VEGF peptides discussed above, we do not agree that the examiner has put forth sufficient argument or evidence that the specification does not enable non-VEGF peptides within the scope of the claims. The specification, pages 20-32, paragraphs [0050] to [0070], describes various classes of subspecies of non-VEGF peptides which, appellants allege, possess angiogenic properties. Many of the subspecies are supported by reference to scientific publications. As we have found that the examiner has not established a prima facie case of lack of enablement in the first instance, we do not reach appellants' evidence in support of enablement. This rejection of the claims for lack of enablement is reversed.

Upon review of the relevant portions of the specification indicated above with respect to enablement, we find such portions also adequately describe the claimed invention. In our view appellants have described the claimed subject matter in the specification clearly enough that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented the subject matter including those limitations. In view of the above, this aspect of the written description rejection is reversed.

3. **Lack of Written Description and Enablement of fusion proteins with specified half-life**

The examiner argues there is no written description of fusion proteins with a half-life of at least twice as long as either the first or second peptide portion or both as in claim 6. The examiner argues that "the specification, as filed, does not disclose the half lives of various proteins, nor does it provide any data or working example of the half-life of any of the claimed fusion proteins", and that the art of increasing half-lives of proteins is unpredictable. Answer, page 11.

Appellants respond arguing that (Brief, page 7)

> methods for determining protein half-life having long been known to those of ordinary skill in the art, and include for example, pulse chase experiments as described in Dandri... and Distelhorst... Moreover the specification discloses specific structural features of the claimed fusion protein, the absence or presence of which enhances protein stability. For example the specification discloses that removal of the Ang-1 coiled-coil domain imparts an increased half-life to a fusion protein comprising Ang-1 as the non-VEGF peptide portion (see, e.g. paragraph [0108], lines 10-14.) The specification also indicates that the inclusion of cysteine residues in either or both of the VEGF and non-VEGF peptide portions of the claimed fusion protein renders the fusion protein more resistant to extracellular degradation... thereby enhancing protein stability. Fusion protein half-life can also be extended when the non-VEGF peptide portion comprises an IgG domain as described in the specification at paragraph [0108], lines 18-22.

The examiner returns, that "it is well known in the art that adding cysteine residues may adversely effect protein folding and activity, and there is no guidance as to where, in any particularly disclosed protein, such cysteine residues could be added." Answer, page 21. We find no evidence of record cited by the examiner to support this

position.

While the examiner presents argument as to what is known in the art the examiner has failed to provide evidence to support this statement. In re Lee, 277 F.3d 1338, 1343-1344, 61 USPQ2d 1430, 1433-1434 (Fed. Cir. 2002). In addition, the examiner has failed to show with appropriate evidence that one of ordinary skill in the art following the disclosure of the specification would be unable to obtain a fusion protein having the claimed half-life or would have required undue experimentation to obtain such a fusion protein. This aspect of rejection of the claims for lack of enablement is reversed.

We remind the examiner, again, that "[t]he claimed subject matter need not be described in haec verba to satisfy the description requirement. It is not necessary that the application describe the claim limitations exactly, but only so clearly that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented processes including those limitations." (citations omitted). See, e.g., In re Herschler, 591 F.2d 693, 700, 200 USPQ 711, 717 (CCPA 1979). See also Purdue Pharma L.P. v. Faulding, Inc., 230 F.3d 1320, 1323, 56 USPQ2d 1481, 1483 (Fed. Cir. 2000) ("In order to satisfy the written description requirement, the disclosure as originally filed does not have to provide in haec verba support for the claimed subject matter at issue.").

Upon review of the relevant portions of the specification indicated above with respect to enablement, we find such portions also adequately describe the claimed invention. In our view appellants have described the claimed subject matter in the specification clearly enough that one having ordinary skill in the pertinent art would recognize from the disclosure that appellants invented the subject matter including those limitations. In view of the above, this aspect of the written description rejection is reversed.

4. **Lack of Written Description and Enablement of fusion proteins described in claim 12**

The examiner argues there is no adequate "written description and enablement to support the scope of fusion proteins that result in vessels that are associated with more smooth muscle cells, a greater concentration of smooth muscle cells, more endothelial cells, a greater concentration thereof, or a combination of such than would be obtained using only the 'VEGF' portion of the protein." Answer, page 11.

The examiner admits that "the only ...property to have been recognized to be associated with HBNF is the proliferation of endothelial cells, and the specification provides no guidance or working examples of HBNF with the other such properties." Answer, page 12. Thus, the examiner admits that the HBNF described in the specification possesses at least one of the claimed properties, proliferation of endothelial cells.

Appellants argue that "the disclosure of angiogenic promoting factors (e.g., HBNF) in the specification and the literature, coupled with the disclosed methods for making and using the claimed fusion protein, clearly equips the skilled artisan with the ability to practice the invention defined by claim 12 using only routine methods of experimentation." Brief, page 8.

Paragraph [0052] of the specification, pages 22-23, provides a listing of peptides which modulate growth, chemotactic behavior, and/or functional activities of smooth muscle cells. These peptides include "Activin A, Adrenomedullin, ANF, Angiotensin-2, Betacellulin, CLAF, endothelins, Factor X, Factor Xa, HB-EGF, Heart derived inhibitor of vascular cell proliferation, IFN-γ, IL1, Leiomyoma-derived growth factor (LDGF), SMC-CF, macrophage derived growth factor (MGDF), monocyte-derived growth factor, Oncostatin M, Prolactin, Protein S, SDGF (smooth muscle cell derived growth factor), SDMF (smooth muscle cell derived migration factor), tachykinins, and Thrombospondin." Id. Peptides which modulate the growth, chemotactic behavior, and/or functional activities of vascular endothelial cells are identified in the specification at page 23, paragraph [0053].

In our view, the examiner has not established with appropriate argument or evidence that one of ordinary skill in the art, upon reading the present specification, would not have been enabled to make or use a fusion protein as in claim 12. We do not find that the examiner has met his burden of showing that undue experimentation would have been required to obtain a fusion protein as set forth in claim 12. The

examiner's analysis does not appear to take into account the above cited paragraphs in the specification that specifically discuss smooth muscle cell and endothelial cell-specific factors. Nor has the examiner set forth a prima facie case of lack of written description with respect to claim 12. Therefore, the rejections of claim 12 for lack of written description and lack of enablement are without merit and are reversed.

5. **Lack of Written Description and Enablement of Properties in Claim 17**

The examiner argues that the properties of the second peptide that it promotes blood vessel wall maturation, blood vessel wall dilatation, blood vessel remodeling, extracellular matrix degradation, decreases blood vessel permeability or any combination thereof is not described or enabled by the specification. Answer, page 12.

These properties are set forth in the specification at pages 19-20, paragraph [0048], and products possessing these properties are disclosed to include, for example, midkine, TNF-α, iNOS, and angiopoietin. Appellants argue that "methods to determine if a potential second peptide portion exhibits any one of the functional characteristics set forth in claim 17 are known in the art and described extensively in the specification, as are methods of generating the claimed fusion protein." Brief, page 8.

Again, this case turns on which party has the burden in the first instance. The examiner has not put forth any evidence which would support her position that the angiogenesis products described in the specification would not have been recognized by those of ordinary skill in the art to possess the functional characteristics described

therein.

Moreover, the examiner indicates in the rejection under 35 U.S.C.§ 102 that "Angiopoietin is known in the art to reduce [vessel] permeability", meeting the limitations of claim 17. Answer, page 13. We do not find the examiner has established a prima facie case of lack of enablement supported by sufficient argument or evidence. As we have found that the examiner has not established a prima facie case of lack of enablement in the first instance, we do not reach appellants' evidence in support of enablement. The rejection of claim 17 for lack of enablement is reversed.

From the above, it would appear that the specification reasonably describes products having the claimed properties. The rejection of claim 17 for lack of written description is reversed.

35 U.S.C. §102(a)

Claims 1-4, 9, 16-19, 32-34, 39-40 and 43-45 stand rejected under 35 U.S.C. § 102(a), as anticipated by Davis.

The examiner argues that (Answer, page 13):

> Davis [ ] disclose fusion proteins comprising the receptor binding domains of two ligands, which ligands may be the same or different, as well as multimers thereof. Preferred embodiments include Angiopoietin-1 and -2, and EPH family ligands, see claims. At page 9 a species comprising VEGF and angiopoietin is specifically described, as is the definition that 'receptor binding domain" is "the minimal portion of the ligand that is necessary to bind it's receptor."

Appellants argue in response, that the Ang-1 peptide portion of the VEGF-Ang-1 fusion protein disclosed in the Davis '642 PCT application does not separately promote angiogenesis or bone growth, as required by ....the claims." Brief, page 9. Appellants argue that, "[t]he Davis '642 PCT application indicates that Ang-1 'clustering' induces or enhances its biological activity." Davis also (Brief, page 10):

> discloses that monomeric Ang-1 has low affinity for the Tie-2 receptor as compared to highly clustered (e.g., tetrameric) VEGF-Ang-1 fusion proteins.
>
> Therefore, the non-VEGF peptide portion of the fusion protein disclosed in the '642 PCT application does not separately promote angiogenesis, bone growth, and/or wound healing, as required by claims 1 and 43, but rather requires multimerization to exert its biological activity.

We do not agree with appellants' characterization of Davis. Davis discloses at page 9, lines 9-14, that the fusion protein may comprise, as a first subunit, the receptor binding domain of VEGF and the second subunit may comprise the receptor binding domain of angiopoietin. "Still further, the first and second subunits may each have one or more than one copy of the receptor binding domain of their respective ligand." Id. Thus Davis appears to describe not only fusion proteins comprising highly clustered proteins but also single subunits having one copy of the receptor binding domain of their respective ligand.

Moreover, the examiner indicates (Answer, pages 24-25) that "VEGF and angiopoietin-1 function together during vascular development, with VEGF acting during early vessel formation, and angiopoietin-1 acting later during vessel remodeling, maturation and stabilization." "Thus, separate from VEGF-1, in the sense that they do

not act together to cause the same effect, Ang-1 clearly promotes angiogenesis, at a later stage in the process than VEGF." Answer, page 24. In addition, the examiner notes that "Ang-1 is specifically disclosed as a species of 2nd peptide, at paragraph [0050] of the specification." Id. We also agree with the examiner that the claims do not require any particular amount of angiogenic or bone growth activity. Answer, page 25.

Thus, we agree that the examiner has established a prima facie case of anticipation over Davis. We do not find that appellants have rebutted the examiner's prima facie case of anticipation with sufficient argument or evidence. Appellants have not provided any evidence showing that Ang-1 does not possess angiogenesis promoting activity.

The rejection of the claims for anticipation over Davis is affirmed.

35 U.S.C. 103(a)

Claims 1-5, 9, 17, 18, 32-34, 41 and 43-46 stand rejected under 35 U.S.C. § 103(a), as obvious over Yoon in view of either or both of Gill and Rockwell.

Yoon teaches an EGF:angiogenin fusion protein. Answer, page 14. According to the examiner, Yoon teaches that because EGF receptors are expressed on most cancer cell lines, EGF can be used to target and internalize the angiogenin portion of the fusion protein, resulting in targeted cytotoxicity. Id. In this regard, Yoon states that "[b]inding of EGF to the extracellular domain of the EGFR activates the receptor

tyrosine kinase, which causes autophosphorylation of the receptor as well as of other substrates, eventually leading to increased cell proliferation. During this process the ligand-receptor complex is internalized into the intracellular compartments where it is degraded... [H]uman angiogenin ... shows RNAse and ribosomal inactivating activities besides its angiogenic activity... Human angiogenin is also a potent inhibitor of protein synthesis in cell free extracts, but extracellular angiogenin is not cytotoxic toward a wide variety of cultured cells." Yoon, p. 1436. The EGF-angiogenin fusion protein "maintained receptor binding activity of EGF and RNase activity of angiogenin in a single peptide and actively inhibited growth of human EGFR-positive target cells in culture." See abstract, page 1435. The examiner notes that the EGF receptor is, like the VEGF receptor, a tyrosine kinase receptor. Answer, pages 14-15. See also Rockwell, Col. 1, lines 60-66.

The examiner acknowledges that Yoon does not teach a fusion protein comprising VEGF and angiogenin. Answer, page 15. To make up for this deficiency, the examiner relies on Gill and Rockwell. Gill teaches that Kaposi's sarcoma (KS) cells express VEGF receptors, and that the cell growth and KS cell survival depend upon VEGF. Rockwell teaches that flk-1 (VEGFR-2, Answer, page 15) receptor expression is probably induced during glioblastoma tumor formation, and that high levels of flk-1 are expressed by endothelial cells that infiltrate gliomas.

The examiner argues (Answer, page 15),

> [i]t would have been obvious to one of ordinary skill in the art at the time the invention was made to substitute VEGF 121 for the EGF in the fusion

> protein of Yoon et al. for the purpose of making a cytotoxic fusion protein to be used to treat either KS or glioma/glioblastomas. The artisan would have been motivated to do so by the disclosures of Gill et al. and Rockwell et al. that the VEGF receptors are 'markers' for those tumors, and would have been particularly motivated to use the 121 amino acid form of VEGF, as it is the shorter of the soluble forms... and the art generally recognizes the utility of using smaller molecules where possible, for example see Yoon et al. Accordingly, the invention, taken as a whole, is prima facie obvious over the cited prior art.

Appellants argue that one of ordinary skill in the art would not be motivated to substitute VEGF for EGF in the fusion protein of Yoon. Brief, page 10. Appellants argue that Yoon teaches away from such a substitution because VEGF is an agent that promotes tumor angiogenesis and one of ordinary skill in the art seeking to kill tumor cells in accordance with the disclosure of Yoon would not be motivated to substitute VEGF for EGF "in as much as the VEGF peptide portion would enhance tumor cell survival by promoting tumor angiogenesis." Id, pages 10-11.

The examiner responds to appellants, arguing, "[a]lthough VEGF would, alone, be contraindicated for administration to a tumor, as a fusion protein with angiogenin, it would be expected to be cytotoxic... and thus *not* cause angiogenesis and further tumor growth." Answer, page 25.

We agree with the examiner that Yoon does not teach away from the substitution of VEGF for EGF in its fusion protein. Both the EGF receptor and the VEGF receptor are tyrosine kinase receptors. See, e.g., Rockwell, Column 1, lines 60-66. Yoon teaches that EGF is a tumor marker for epithelial carcinoma cells and CHO-K1 cells. Gill and Rockwell teach that VEGF is a tumor marker for KS and glioma/glioblastoma.

Thus, we agree with the examiner that Gill and Rockwell provide motivation to substitute VEGF tumor markers for the EGF tumor marker of Yoon in the cytotoxic fusion protein of Yoon for the purpose of treating KS and glioblastoma.

We acknowledge that the appellants' motivation for preparing the claimed fusion protein is to produce a final end product which promotes angiogenesis and/or wound healing. However, appellants should also keep in mind, that the so-called motivation to combine references does not have to be identical to the appellants' to establish obviousness. In re Kemps, 97 F.3d 1427, 1430, 40 USPQ2d 1309, 1311 (Fed. Cir. 1996). Therefore, the fact that Yoon combines two angiogenesis promoting peptides to effect cellular cytotoxicity is of no consequence, as Yoon provides an alternative motivation for combination with Gill and Rockwell.

Moreover, we do not find any argument or evidence put forth by appellants establishing that VEGF, a tyrosine kinase receptor similar to EGF, would not be internalized into the cell or function in the same manner as EGF, as described in the fusion protein of Yoon.

After evidence or arguments are submitted by the appellant in response to rejection based on obviousness, patentability is determined on the totality of the record, by a preponderance of evidence with due consideration to persuasiveness of the argument. On balance, we believe that the totality of the evidence presented by the examiner and appellants weighs in favor of finding the claimed invention is obvious in view of the combination of Yoon with Gill and Rockwell. The rejection of claims 1-5, 9,

17, 18, 32-34, 41, and 43-46 for obviousness is affirmed.

CONCLUSION

We reverse the enablement and written description rejections except for that of claim 12, which we affirm. We affirm the rejection of claims 1-4, 9, 16-19, 32-34, 39-40 and 43-45 under 35 U.S.C. § 102(a), as anticipated by Davis; and the rejection of claims 1-5, 9, 17, 18, 32-34, 41 and 43-46 under 35 U.S.C. § 103(a), as obvious over Yoon in view of either or both of Gill and Rockwell. In view of our decision in this appeal, claims 6, and 7 are not rejected.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 CFR § 1.136(a).

AFFIRMED-IN-PART

DONALD E. ADAMS Administrative Patent Judge	)
DEMETRA J. MILLS Administrative Patent Judge	) BOARD OF PATENT) APPEALS AND) INTERFERENCES
ERIC GRIMES Administrative Patent Judge	)

Appeal No. 2004-1259
Application No. 09/832,355

LEYDIG, VOIT & MAYER, LTD.
Two Prudential Plaza, Suite 4900
180 N. Stetson Ave.
Chicago, IL 60601-6780